

REMARKS

Reconsideration of this application, as amended, is respectfully requested.

Claims 44-48, 73, 75-77, 81-82 and newly inserted claims 83-93 are pending. Claims 1-43, 49-72, 74 and 78-80 have been canceled without prejudice or disclaimer. Applicants hereby explicitly preserve the rights to pursue all canceled subject matter in one or more future applications. Claim 44 is amended to further clarify the claim. The amendments and new claims are fully supported by the originally filed specification, for example, on page 5, last paragraph; page 21, second paragraph step (c); and examples 1-5. Thus, the amendments do not constitute new matter.

A. Withdrawal of Previous Rejections

Applicants thank the Office for withdrawing previously raised rejections under 35 U.S.C. section 112, second paragraph, and sections 102(a) and 103.

B. Priority

The Action has acknowledged Applicants' claim to foreign priority under 35 U.S.C. 119(a)-(d) to Application No. 198 27 714.8, filed on June 22, 1998 ("the '714 Application"), and to Application No. 198 38 802.0, filed on August 26, 1998 ("the '802 Application"). Acknowledgement was also made by the Office to the receipt of certified translations of these two foreign priority applications. The Action, however, asserts that the previously submitted claims are not entitled to the earlier priority dates. Specifically, the Action asserts that the earlier disclosures only teach a sample-specific cutoff and not a test area-specific cutoff. Further, the Action asserts that the claim reciting the detection of a pathogen based on a positive result obtained from at least one of the test areas is not entitled to either of the earlier priority dates. The Action takes the position that the '714 Application requires that "two or more test areas must be positive" to indicate a positive result. *See* page 6 of the Office Action. Thus, the Office has set the priority date of the instant application only to the utility filing date June 22, 1999.

Applicants respectfully disagree. Without acquiescing to the assertions or the basis for the assertions, Applicants have amended claim 44 (c) to recite:

detecting and separately measuring presence or amount of a signal generated by the signal generating group bound to the first and second test areas wherein the signal above a predetermined test area-specific cutoff is classified as positive and below a predetermined test area-specific cutoff as negative, and wherein a positive signal obtained from at least one of the first and second test areas is indicative of the presence of an analyte of the plurality of analytes and is indicative of the presence of the pathogen in the sample.

Support for the amended claims can be found in the earlier disclosure. *See* for example, page 20, lines 12-18 of the '802 Application. A test area-specific cutoff or threshold value is also expressively disclosed in the '802 Application. *See* page 11, second paragraph. Throughout this response, all citations to the priority applications refer to the page numbering of the English translations of the priority applications.

Further, Applicants disagree with the Action's assertion that, based on the '714 Application, two or more assay areas must be positive for a result to be considered positive. The Action cites to page 6, first paragraph of the '714 Application as support for the assertion. The relevant section states:

If a positive assay result is obtained on two or more assay areas, this is assessed as the presence of the analyte in the sample.

Thus, positive results obtained from two or more assay areas would indicate the presence of a pathogen, such as HIV, in a sample. The '714 Application, however, never *requires* that the presence of a pathogen in a sample is determined only if two or more test areas are positive. To the contrary, the '714 Application clearly indicates that a positive signal obtained from at least one of the test areas is sufficient for a detection of the pathogen. This is supported by the data shown in Example 2 of the '714 Application, in which the inventive method demonstrated earlier detection of HIV in six samplings as compared to the results obtained by Western blot assay. *See* page 22, lines 9-12 of the '714 Application. Only two of the six samplings exhibited positivity in two test areas, while the remaining four samplings each exhibited positivity in only one test area. *See* Table bridging pages 21 and 22. Thus, the disclosure of the '714 Application supports that a positive result obtained from at least one test area is sufficient for a positive detection of a pathogen in a sample. Similar disclosure can be found on pages 23 and 24 of the '802 Application. Thus, the recitation "wherein a positive signal obtained from at least one of the first and second test areas is indicative of the presence of an analyte of the plurality of analytes and

is indicative of the presence of the pathogen in the sample” is supported by the priority applications and entitled to the earlier filing dates.

In summary, the currently pending claims are supported by at least the disclosure of the ‘802 Application, and are entitled to at least the priority date of August 26, 1998.

C. Rejections under 35 U.S.C. §112, First Paragraph, Written Description

Claims 44-48, 73, 75-77, and 81-82 stand rejected for allegedly failing to comply with the written description requirement under 35 U.S.C. § 112, first paragraph. Specifically, the Action asserts that the specification does not support the manner in which the test area-specific background is measured as recited in claim 44 step (d).

Applicants respectfully traverse the rejection. Without acquiescing to the Action’s assertions, Applicants have nevertheless deleted claim 44 step (d). Thus, the amendment has rendered the rejection moot.

D. Rejections under 35 U.S.C. §112, Second Paragraph

The Action rejects Claims 44-48, 73, 75-77, and 81-82 for allegedly being indefinite under 35 U.S.C. § 112, second paragraph. Specifically, the Action asserts that it is unclear how background measurements could be performed on the first and second test areas in the absence of analyte as recited in claim 44 step (d) when these same test areas have been previously contacted with analytes.

Applicants respectfully traverse the rejection. Without acquiescing to the Action’s assertions, Applicants have nevertheless deleted claim 44 step (d). Thus, the amendment has rendered the rejection moot.

E. Rejections under 35 U.S.C. §103(a)

The Action raises several rejections under 35 U.S.C. § 103(a) of claims 44-48, 73, 75-77, and 81-82 as being obvious. Specific rejections are listed below.

1. Claim rejection under 35 U.S.C. § 103(a) based on Karl

In paragraph 17 of the Action, Claims 44, 46-48, 73, 76-77 and 81 stand rejected under 35 USC § 103(a) as being obvious over Karl *et al.* (WO 99/05525) (“Karl”). Without acquiescing to the basis for the assertions by the Action, Applicants respectfully point out that Karl is disqualified as prior art under the provisions of 35 U.S.C. § 102.

Karl was published on February 4, 1999 and was previously cited by the Office as prior art under 35 U.S.C. § 102(a). *See* page 9 of the Office Action dated February 4, 2009. As stated above, the currently pending claims are entitled to the priority date of at least August 26, 1998, the filing date of the ‘802 Application, which predates the publication date of Karl. Thus, Karl is disqualified as prior art with respect to the currently pending claims.

Thus, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 103(a) based on Karl.

2. Claim rejection under 35 U.S.C. § 103(a) based on Karl in view of Schonbrunner

In paragraph 18 of the Action, claims 45 and 75 stand rejected as being unpatentable over Karl in view of Schonbrunner (GB 2 313 666A). Specifically, the Action asserts that Karl teaches a method in which a sample is simultaneously analyzed to determine multiple analytes on a single solid phase. While acknowledging that Karl does not teach simultaneous detection of HIV antibodies and HIV antigens, the Action nevertheless asserts that Schonbrunner cures the defects. Applicants respectfully traverse the rejections. Claims 45 and 75 ultimately depend on claim 44 and include all limitations of claim 44.

A claimed invention is unpatentable if the differences between it and the prior art “are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art.” 35 U.S.C. § 103(a); *see Graham v. John Deere Co.*, 383 U.S. 1, 14 (1966). The ultimate determination of whether an invention is or is not obvious is based on underlying factual inquiries including: (1) determining the scope and content of the prior art; (2) ascertaining the differences between the prior art and the claims at issue; (3) resolving the level of ordinary skill in the pertinent art; and (4) evaluating evidence of secondary considerations. *See Graham*, 383 U.S. at 17-18.

The Supreme Court emphasizes that the key of supporting any rejection under 35 U.S.C. §103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. *KSR Int’l Co. v. Teleflex Inc.*, 127 U.S. 1727, 1741 (2007). The Court, quoting *In re Kahn*, stated that “rejections on obviousness cannot be sustained with mere conclusory statements;

instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” *In re Kahn*, 441, F.3d 977, 988 (Fed. Cir. 2006). In addition, a combination of references must teach every element of the claims to render the claims obvious. *See Honeywell International, Inc. v. United States*, 93 U.S.P.Q. 2d 1740, 1747 (Fed. Cir. 2010) (holding that the claims are not obvious because the combination of references fails to teach one element of the claim).

As stated above, Karl is disqualified as prior art. Schonbrunner alone would not have rendered the subject matter of claims 45 and 75 obvious. For example, Schonbrunner does not teach or suggest a test area-specific cutoff, and the Action does not state otherwise. Thus, Schonbrunner does not teach every element of the claims and the Action has not articulated any reasons as to why the missing element would have been obvious to one of ordinary skill in the art. Accordingly, the claims are not obvious in light of Schonbrunner, and Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 103(a).

3. Claim rejection under 35 U.S.C. § 103(a) based on O'Connor in view of Osther, and either Bayer or Tidey

In paragraph 19 of the Action, claims 44-45, 47-48, 73, 75-77 and 81 stand rejected under 35 U.S.C. § 103(a) over O'Connor et al. (U.S. 5,627,026) (“O'Connor”) in view of Osther et al. (U.S. 5,008,813) (“Osther”), and either Bayer et al. (CA 2109239) (“Bayer”) or Tidey et al. (U.S. 6,046,013) (“Tidey”). Specifically, the Action asserts that O'Connor teaches a solid support containing a first location with an antigen capable of selectively forming an immune complex with a sample antibody bound thereto, and a separate location with an antibody capable of selectively forming an immune complex with a sample antigen bound thereto. The Action further asserts that O'Connor discloses measuring signals from the negative controls, in which antigen-coated wells were contacted with samples known not to contain analyte and the absorbance intensity of each well was compared to the negative control. The Action, however, acknowledges that O'Connor fails to teach the use of a negative control sample in a context other than an HIV antibody ELISA test, and thus “fails to specifically illustrate measuring a ‘test area-specific’ background measured on the first or second test area.” *See* page 19 of the Office Action (emphasis in original).

The Action nevertheless asserts that Osther and either Bayer or Tidey cure the defects. Specifically, the Action cites to Osther for the proposition that one of ordinary skill in the art

recognized the value of negative controls in providing information about the particular analyte-specific receptor being used to detect analytes as well as in establishing a cutoff point. It is without dispute that Osther does not teach a test area-specific cutoff, nor does the Office assert otherwise.

With regard to Bayer or Tidey, the Action asserts that either reference teaches measuring a test area-specific background when detecting a plurality of analytes. Applicants respectfully disagree and address each reference in turn as follows.

- a. Bayer does not and cannot teach a test area-specific cutoff for each analyte-specific receptor because Bayer teaches one test area that contains multiple analyte-specific receptors

The Office's reliance on Bayer for the purported disclosure of a test area-specific cutoff is misplaced. Bayer merely relates to detection of antigens and antibodies using respective receptors, *e.g.*, using an antibody receptor R1 for detecting an antigen, and an antigen receptor R2 for detecting an antibody. Bayer, however, does not teach that R1 and R2 are immobilized on *separate* solid phases, *i.e.*, *separate* test areas. This is evident throughout the disclosure of Bayer, which states that “a solid phase is used on the surface of which the receptors R1 and R2 are directly bound or can be bound.” (Emphasis added.) *See* p. 5, lns. 19-21; p. 14, lns. 13-15; and claims 1 and 33. Nowhere in the disclosure does Bayer explicitly teach “at least two separate” solid phases or “at least two separate” test areas. Because R1 and R2 are bound to the one solid phase, Bayer does not and cannot teach or suggest a test area-specific background or a test area-specific cutoff.

Bayer describes the superiority of a detection method for detecting the presence of a pathogen based on a *sum* of the simultaneously measured signals derived from the binding of the antigens and antibodies to their respective receptors, and not individually measured signals obtained from separate test areas. For example, Bayer states on page 4, second paragraph:

Samples with a low content of antigens and antibodies which yield borderline signals when the antigens or antibodies are determined separately, i.e., signals which are near to the detection limit and which may be falsely classified as negative or require a repeated determination, can be classified as positive using the method according to the present invention.

The asserted advantages of Bayer's method was purportedly demonstrated by the results shown in Table 1, which was explicitly cited to in the Action and presumably considered by the Office. Table 1 showed that for a serum sample that yielded borderline signals and therefore may be falsely classified as negative when the antigens or antibodies were determined separately was correctly classified as positive when a *summation* of signals measuring the presence of p24 antigen, and anti-gp120, anti-gp41, and anti-gp32 antibodies was obtained.

According to Bayer's method, all analyte-specific receptors were immobilized on one solid phase and thus one test area. Therefore, a separate determination of test area-specific cutoff for each analyte-specific receptor is simply impossible. This is evident from the results in Table 1, where only one negative control cutoff value was provided (*i.e.*, 62) when p24 antigen, anti-gp120, anti-gp41, and anti-gp32 antibodies were measured simultaneously.

What Bayer does not disclose, but was known in the art, is that when a plurality of analytes are measured based on one negative control cutoff, the cutoff value must be set relatively high to take into account the analyte-specific receptor that exhibits the worst cross-reactivity. *See* page 3, second paragraph of the instant specification. Setting a high cutoff may lead to reduced sensitivity of the assay, which is precisely one of the drawbacks of the conventional methods that the claimed method has overcome by using a *test area-specific cutoff for each analyte-specific receptor*. Thus, the Bayer method is what the claimed invention intends to avoid, and one of ordinary skill in the art would not have resorted to Bayer in order to overcome the problems known in the art.

Further, one of ordinary skill in the art would not have been motivated to drastically modify Bayer to arrive at the instant invention. Doing so would require the skilled in the art to intentionally ignore Bayer's explicit teachings that separate measurement of each analyte would likely lead to false negative results. Such explicit teachings of Bayer's in fact teach away one of ordinary skill in the art from attempting the instantly claimed invention.

Finally, even if, assuming *arguendo*, a skilled artisan would have considered Bayer, the combination of O'Connor, Osther and Bayer still does not teach a test area-specific cutoff, and thus does not teach every element of the claims. And the Action has not articulated any reasons as to why the missing element would have been obvious to one of ordinary skill in the art. Based on the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) over O'Connor in view of Osther and Bayer.

- b. Similarly, Tidey does not and cannot teach a test area-specific cutoff for each analyte-specific receptor because each test area contains multiple analyte-specific receptors

The Action asserts that Tidey teaches “testing serum samples for reactivity with forty wells (test areas) containing a specific HLA molecule.” See page 20 of the Office Action. In addition, Tidey purportedly teaches obtaining different background levels for each HLA molecule to be used as cutoffs for the purpose of validating the test results. Thus, the Action asserts that it would have been obvious to one of skill in the art to relate the signal value of the sample to the signal value of the negative control for each test area for the purpose of validating the assay. Applicants respectfully disagree.

Similar to Bayer, Tidey concerns a detection assay that is fundamentally different from the instant application. Tidey relates to a method for determining whether a patient’s serum sample contains any anti-HLA antibodies by contacting the sample with different HLA preparations obtained from different donors. As explained below, Tidey does not teach, *inter alia*, (1) a detection method wherein each spatially separate test area having no more than one type of analyte-specific receptor bound thereto; (2) a detection method wherein the signal above a predetermined test area-specific cutoff is classified as positive, and below the predetermined test area-specific cutoff as negative with regard to a specific analyte of a plurality of analytes; thus, (3) a test area-specific cutoff in the sense that the cutoff can be used to validate the detection of a particular analyte in a sample; and (4) a detection method wherein a positive signal obtained from at least one of the first and second test areas is indicative of the presence of an analyte of the plurality of analytes, let alone indicative of the presence of a pathogen in the sample.

The HLA preparations obtained from individual donor were each immobilized onto each well of a microplate. Each HLA preparation, however, comprises not only one analyte-specific receptor for one type of analyte, but *multiple types of receptors for multiple types of analytes*. This is because each donor’s white blood cells carry eight types of HLA Class I tissue antigens and two types of Class II tissue antigens. See col. 1, lines 46-52 of Tidey. Thus, the HLA preparation obtained from each donor naturally comprises multiple types of HLA antigens that potentially can be bound by multiple types of antibodies if present in a sample. Therefore, in Tidey, each test area contains multiple types of analyte-specific receptors for a plurality of analytes. Thus, Tidey does not and cannot teach or suggest “each spatially separate test area having no more than one type of analyte-specific receptor bound thereto” as required in claim 44.

As a result, the purported test area-specific background calculated in Tidey does not represent a background level for *a particular type of HLA antigen* in an immunoassay; rather, the purported test area-specific background at best represents a background level of *a collection of* HLA antigen types that are present in a particular HLA preparation obtained from a particular donor. Thus, Tidey does not and cannot teach a test area-specific cutoff in the sense that the cutoff can be used to validate the detection of a particular analyte in a sample.

Further, in Tidey, a positive result obtained from one test area indicates the presence in the sample of one or more types of antibodies specific for one or more types of HLA antigens that are immobilized on the test area. Thus, Tidey does not and cannot teach or suggest a test area-specific cutoff wherein the signal above the predetermined test area-specific cutoff is classified as positive for *a particular analyte*, and below the predetermined test area-specific cutoff as negative for *a particular analyte*, of a plurality of analytes.

In addition, it is clear from Tidey that a positive result obtained from *one* test area alone, is insufficient for a determination of the presence of a particular analyte of a plurality of analytes. This is evident from Example 4 of Tidey, where the detection of the presence of anti-HLA 3 antibody was determined only after positive results were obtained from multiple test areas, on which HLA 3 was the common HLA antigen present. *See* Table of Example 4. Tidey admits that discerning the presence of an antibody to a particular HLA antigen is difficult in the absence of a common HLA antigen. *See* col. 13, lines 19-24. In fact, it is nearly impossible to discern the presence of a specific analyte, *i.e.*, an antibody specific for a particular HLA antigen, based on a positive result obtained from only one test area according to the method of Tidey. Accordingly, Tidey does not and cannot teach or suggest a detection method wherein a positive signal obtained from at least one of the first and second test areas is indicative of the presence of a particular analyte of the plurality of analytes, let alone indicative of the presence of a pathogen in the sample.

Therefore, the method described in Tidey is fundamentally different from the claimed methods. One of ordinary skill in the art would not have been motivated to combine O'Connor and Oster with Tidey to arrive at the claimed invention. Even if, assuming *arguendo*, there is a motivation to combine, the combination of references still does not teach a test area-specific cutoff in the sense that the cutoff can be used to validate the detection of a particular analyte in a sample. Thus, even the combination of O'Connor, Oster and Tidey does not teach every element of the claims and thus does not render the claimed method obvious. *Honeywell International, Inc. v. United States*, 93 U.S.P.Q. 2d 1740, 1747 (Fed. Cir. 2010) (holding that the

claims are not obvious because the combination of references fail to teach every element of the claims). And the Action has not articulated any reasons as to why the missing element would have been obvious to one of ordinary skill in the art.

Thus, the claimed method as recited in claim 44 and dependent claims 45, 47-48, 73, 75-77 and 81 would not have been obvious to one of ordinary skill in the art based on O'Connor, in view of Osther, and further in view of either Bayer or Tidey.

4. Claim rejection under 35 U.S.C. § 103(a) based on O'Connor in view of Osther, and either Bayer or Tidey and further in view of Ekins

In paragraph 20 of the Action, claim 46 stands rejected under 35 U.S.C. § 103(a) as unpatentable over O'Connor in view of Osther and either Bayer or Tidey and further in view of Ekins (U.S. 5,837,551). Claim 46 depends on claim 44 with a further limitation that each test area has a diameter of 0.01 to 1 mm. The Action asserts that while O'Connor does not teach a test area with a diameter of 0.01- 1 mm, Ekins teaches microspots with diameter of 80 microns or 0.08 mm.

Applicants respectfully traverse the rejection. As discussed above, the Action has acknowledged that O'Connor does not teach detecting a test area-specific cutoff. Neither does any one of Osther, Bayer and Tidey, alone or in combination. Ekins merely relates to the size of the test areas and not a test area-specific cutoff. Ekins certainly does not cure the defects. Thus, the combination of art does not teach every element of the claim and the Action has not explained the reasons why the missing element would have been obvious to one of ordinary skill in the art. Accordingly, Applicants respectfully submit that claim 46 is not obvious over O'Connor in view of Osther, Bayer or Tidey, and further in view of Ekins. Reconsideration and withdrawal of the rejection is thus respectfully requested.

5. Claim rejection under 35 U.S.C. § 103(a) based on O'Connor in view of Osther and either Bayer or Tidey and further in view of Miyamura, or alternatively based on Karl, in view of O'Connor and Miyamura

In paragraph 21 of the Action, claim 82 is rejected under 35 U.S.C. § 103(a) as unpatentable over O'Connor in view of Osther and either Bayer or Tidey and further in view of Miyamura et al. (U.S. 5,714,314) ("Miyamura"). Claim 82 depends on claim 44 wherein the plurality of analytes is human hepatitis C virus (HCV) antibodies or antigens.

Specifically, the Action asserts that while O'Connor does not teach detection of HCV antigens and antibodies, Miyamura teaches that prevention, early diagnosis and treatment of HCV infection were important. Thus, the Action reasons that it would have been obvious to one of skill in the art to select HCV as the type of viral infection in the method for simultaneous assay for antigens and antibodies as taught by O'Connor.

Applicants traverse the rejection. As discussed above, the Action has acknowledged that O'Connor does not teach a test area-specific cutoff. Neither does any one of Osther, Bayer and Tidey, alone or in combination. Miyamura merely relates to the detection of HCV antibodies or antigens and does not teach or suggest a test area-specific cutoff. Thus, the combination of art does not teach every element of the claim, and the Action has not explained the reasons why the missing element would have been obvious to one of ordinary skill in the art. Accordingly, Applicants respectfully submit that claim 82 is not obvious over O'Connor in view of Osther, Bayer or Tidey, and further in view of Miyamura. Reconsideration and withdrawal of the rejection is thus respectfully requested.

Alternatively, the Action rejects claim 82 as being unpatentable over Karl in view of O'Connor and Miyamura. Applicants respectfully traverse the rejection. As stated above, Karl is disqualified as prior art. Thus, only O'Connor and Miyamura are discussed.

As admitted by the Office, O'Connor does not teach or suggest measuring a test area-specific background on the first or second test area. Neither does any one of Osther, Bayer or Tidey, alone or in combination. Even if one of ordinary skill in the art would have chosen to detect HCV antigens and antibodies by using the method of O'Connor, claim 82 is not obvious because the combination of O'Connor and Miyamura does not teach the claimed test area-specific cutoff. Accordingly, Applicants respectfully submit that claim 82 is not obvious over O'Connor in view of Miyamura. Reconsideration and withdrawal of the rejection is thus respectfully requested.

Based on the above, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 103(a).

Conclusion

Reconsideration of this application is respectfully requested and a favorable determination is earnestly solicited. The Examiner is invited to contact the Applicants' undersigned representative at (312) 913-0001 if the Examiner believes that this would be helpful in expediting prosecution of this application.

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Respectfully,

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